Oncolytic Viruses to Treat Ovarian Cancer Patients – a Review of Results From Clinical Trials

Onkolytische Viren zur Behandlung von Ovarialkarzinompatientinnen – Eine Übersicht der Ergebnisse klinischer Studien

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Abstract

Oncolytic viruses are replication competent "live" viruses. They infect tumor cells, replicate highly selective inside and thereby destroy them. Because of the enormous advances in the field of genetic engineering and biotechnology during the last decade, virotherapy is increasingly used within clinical trials and proved to be safe and effective. In particular, treatment of ovarian cancer patients is one main focus of research. On the one hand, this is due to the poor prognosis of this dismal entity, resulting in the urgent need for novel therapeutics. On the other hand, as ovarian cancer typically spreads within the peritoneal cavity, intraperitoneal administration of oncolytic viruses is feasible. This paper provides an overview of promising results from clinical trials to treat ovarian cancer patients with oncolytic viruses.

Zusammenfassung

Onkolytische Viren sind replikationsfähige „lebende" Viren. Sie infizieren hochselektiv Tumorzellen, vermehren sich in diesen und zerstören sie dabei. Aufgrund der enormen Fortschritte auf dem Gebiet der Gen- und Biotechnologie kommt die Virotherapie zunehmend in klinischen Studien zum Einsatz und erweist sich als äußerst sicher, nebenwirkungsarm und effektiv. Insbesondere findet sich bei der Behandlung von Ovarialkarzinompatientinnen ein wichtiger Forschungsschwerpunkt. Zum einen liegt dies an der schlechten Prognose der Erkrankung und der hieraus resultierenden Notwendigkeit neuer Therapiemodalitäten. Zum anderen breitet sich das Ovarialkarzinom typischerweise lokoregionär aus, woraus sich die spezielle Möglichkeit der intraperitonealen Applikation onkolytischer Viren ergibt. Die vorliegende Arbeit fasst die vielversprechenden Ergebnisse klinischer Studien zur Behandlung von Ovarialkarzinompatientinnen mit onkolytischen Viren zuammen.

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Introduction

Every year, around 9600 women in Germany develop ovarian cancer. This makes it the fifth most common type of cancer in women. Because of its rare symptoms, 65% of the cases are diagnosed at a very late stage (FIGO III–IV) [1]. Despite advanced surgical techniques and modern systemic therapies (chemotherapy, targeted biological therapies), the 5-year probability of survival (around 30%) has barely improved at all over recent decades [2,3]. New therapeutic approaches are therefore urgently needed.

The treatment of ovarian cancers using oncolytic viruses offers a very promising approach [4]. These are "living" agents which specifically infect and kill tumour cells as part of the virus replication process. Huge numbers of progeny virions are released, which in turn attack further tumour cells. The capability of constant, tumour-specific replication is a property that sets virotherapy apart from classical gene therapy, in which viral vectors that are *not able* to replicate are used to insert foreign genetic material into cells. Moreover, oncolytic viruses can also be used as "gene carriers" to enhance their antineoplastic effects. In contrast to classic gene therapy, the therapeutic transgene, coupled with the viral vector from which it is coded, spreads out within the tumour. This overcomes the hitherto primary transduction inefficiency of tumour cells, a significant limitation in gene therapy for cancer [5].

The use of oncolytic viruses to treat tumours is not a new idea. Interestingly, viruses with natural

oncolytic properties were first described at the start of the last century; a retrospective of the history of virotherapy can be found in Kelly et al. [6]. In the mid-20th century, cases of spontaneous tumour remission were reported following natural infection with measles virus [7,8]. Clinical trials and case studies followed in which adenoviruses or the Newcastle Disease Virus (NDV) were used, among others, to treat tumours [9,10]. However, the inadequate effectiveness, a lack of tumour specificity and dose-limiting side effects made it clear, that a comprehensive understanding of how oncolytic viruses work would be essential if they were to be used in clinical practice. Since the capability for the genetic characterisation and manipulation of viral vectors did not exist in those early days, virotherapy has only experienced a renaissance since the start of the rapid developments in the field of gene- and biotechnology in the 1990s. Now, both the tumour selectivity and the anti-neoplastic properties of oncolytic viruses can be specifically manipulated and optimised. As a consequence hundreds of patients are able to take part in prospective clinical virotherapy studies (including phase III), today [11].

This paper offers an overview of oncolytic viruses that are used in clinical studies to treat patients with ovarian cancer. The basic principles of virotherapy and its particular characteristics are also explained. Future challenges and the potential that oncolytic viruses offer will then be discussed.

Mechanisms of Tumour Selectivity

Throughout evolution, viruses have excelled at specialising in penetrating host cells and appropriating their biosynthetic apparatus. Thereby, they manipulate essential cell functions such as cell division, differentiation and cell death.

These cellular changes are frequently very similar to the changes that a cell experiences during carcinogenesis (e.g. inactivation of the tumour suppressor gene p53, manipulation of the interferon system, stimulation of the cell cycle, suppression of apoptosis) [12]. This is one of the reasons why various viruses prefer to grow in tumour cells. Viruses with natural oncolytic properties include Newcastle Disease viruses (NDV) [13], Vaccinia viruses VV [14], vesicular stomatitis viruses (VSV) [15], parvovirus H1 (H-1PV) [16], measles vaccine viruses (MeV) [17] and reoviruses (RV) [18]. Viruses can also be genetically engineered so that they are dependent on neoplastic host cells to reproduce. This is achieved by (1) modifying the viral envelope to allow selective uptake into tumour cells, (2) disabling a gene needed for efficient replication in normal cells but which neoplastic cells can do without, and (3) creating tumour or tissue-specific promoters that regulate the expression of viral genes [12]. It is also possible to combine these approaches [19]. **Table 1** provides an overview of oncolytic viruses that are already used in clinical studies to treat patients with ovarian cancer.

Viruses with Natural Tumour Selectivity

Living viruses capable of replication have already been used millions of times in the context of vaccination and are known to be extremely safe therapeutic agents with low side effects [20]. The use of “live” vaccine viruses for oncolytic virotherapy therefore would seem to be an elegant approach. Interestingly, some vaccine strains replicate better in neoplastic cells than the corresponding wild type viruses. Measles vaccine viruses, for example, have natural oncolytic properties. In contrast to wild type measles virus they predominately enter cells via the CD46 receptor which is over-expressed by malignant cells including ovarian cancer [21,22]. An innovative approach was described by Peng et al at the Mayo Clinic in Rochester, USA: they generated a measles vaccine virus encoding for the human carcino-embryonic antigen (CEA) (MeV-CEA) [23]. During virotherapy with MeV-CEA, a simple blood test can be taken to determine the CEA level, thereby allowing viral replication to be monitored in real time. Galanis et al. recently published the results of a phase I trial on the intraperitoneal use of MeV-CEA in patients with advanced ovarian cancer [24]. The virus application was well tolerated, could easily be monitored by determining serum CEA levels and demonstrated promising clinical activity.

Another vaccine virus, the Vaccinia virus (VV), has successfully been used to treat smallpox. Numerous clinical studies have also demonstrated that VV has natural oncolytic properties [25–28]. The use of VV for oncolytic virotherapy is regarded as very safe and generally only causes mild, flu-like symptoms. Disabling two viral genes enhances tumor selectivity: thymidine kinase (TK) enables the virus to replicate independently of the host cell’s cell cycle, and the Vaccinia growth factor (VGF, similar to the epidermal growth factor EGF) makes it easier for the virus to infect neighbouring cells [29]. Both TK and EGF are over-expressed by many tumour cells, which is why their deletion within the VV genome makes virus replication more difficult in non-neoplastic cells, while neoplastic cells are able to produce large volumes of progeny viruses. Pre-clinical studies using VV to treat ovarian cancer demonstrated an excellent anti-tumour activity [30]. In view of the large virus genome, VV is also an excellent vector for

Tab. 1 Oncolytic viruses that have been used in clinical phase 1 studies on the treatment of patients with ovarian cancer.

Virus	Name	Mechanism of tumour selectivity	Result	Reference
Measles vaccine virus	MeV-CEA	Natural tumour selectivity	Good tolerance. Dose-dependent stabilisation of the progress of the disease in 14 out of 21 patients with an average duration of 93 days.	[24]
Adenovirus	Onyx-015	Deletion in the E1B and E3B gene (tumour selectivity for cells with defective p53 signal transduction pathway and defective RNA transport)	Good tolerance. No clear radiological or clinical tumour response.	[39]
	H101	Deletion in the E1B and E3B gene (tumour selectivity for cells with defective p53 signal transduction pathway and defective RNA transport)	Good tolerance. 3/9 patients with complete remission, 2/9 with partial remission and 4/9 with no tumour response.	[40]
	Ad5-delta24-RGD	Binds to αvβ3 and αvβ5 integrins; deletion in the E1A gene (tumour selectivity for cells with defective retinoblastoma protein-dependent cell cycle control)	Good tolerance. 15/21 patients with stable disease, 6/21 with progressive disease and 7/21 with decreasing CA125.	[42]

additional therapeutic transgenes. Chalikonda et al. generated a VV encoding for the suicide gene cytosine deaminase (CD) (vvDD-CD). This converts the non-toxic prodrug 5-FC into cytotoxic 5-FU. In an animal model to treat ovarian cancer, the addition of the prodrug increased the oncolytic activity of vvDD-CD in a tumour-specific and highly significant manner [31].

Multiple phase I/II clinical trials using VV are currently being carried out on the treatment of ovarian cancer (http://www.jenerex.com). Currently, the first german virotherapy phase I trial to treat therapy resistant peritoneal carcinosis is initiated, which includes a large proportion of ovarian cancer patients with peritoneal recurrence (http://www.clinicaltrials.gov/ct2/show/NCT01443260?term=GL-ONC1&ra=1).

One of the first virotherapy approaches for the treatment of ovarian cancer was the use of oncolytic reoviruses. These double-stranded RNA viruses replicate highly selectively in tumour cells with an activated Ras signal transduction pathway. Hirasawa et al. demonstrated in animal models that reoviruses are able to shrink ovarian cancer, reduce the formation of ascites and significantly prolong the survival of animals given this treatment [32]. Reoviruses of serotype 3 (Reolysin®, Oncolytics Biotech) are currently being used in numerous clinical phase I and II trials that include to treat advanced ovarian cancer (http://www.clinicaltrials.gov/ct2/results?term=Reolysin) [33]. Following both, intraperitoneal and intravenous virus application, there was excellent tolerance, tumour-specific viral replication and oncolytic activity [34,35].

Viruses with Genetically-Engineered Tumour Selectivity

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In many cases, viral gene products require the proliferation of the host cell or inhibit anti-viral defence mechanisms. Since tumour cells proliferate actively and frequently have limited viral defences, the disabling of certain viral genes brings about artificial tumour selectivity. Consequently, the adenoviral protein E1B binds to and inactivates tumour suppressor p53, thereby promoting continuous viral replication [36]. Disabling E1B accordingly leads to the targeted infection of cells with defective p53 signal transduction pathway. Both adenoviruses Onyx-015 and H101 (Sunway Biotech, Shanghai, China) have corresponding deletions in the E1B gene [37,38]. Onyx-015 was the first genetically modified oncolytic virus to be used in clinical studies. Although the virus demonstrated promising oncolytic activities in pre-clinical studies, a phase I trial on the treatment of patients with ovarian carcinoma showed no clear clinical or radiological tumour response [39]. H101 is the first oncolytic virus to receive market approval (in China, not in western countries) based on phase III trials. A phase I trial on the treatment of malignant ascites in ovarian cancer patients led to a significant reduction in the frequency of paracentesis, which markedly improves quality of life [40].

The primary point of attack for the adenoviruses mentioned is the Coxsackie adenovirus receptor (CAR). The reason for the inadequate clinical effectiveness of Onyx-015 in the treatment of ovarian cancer may be the highly variable expression of CAR and a resulting inadequate transduction efficiency of the addressed tumour cells. Genetic modifications of the viral envelope may accordingly lead to an increased binding affinity towards ovarian cancer cells. The adenovirus Ad-delta24-RGD, for example, binds to integrins in the cell surface, including those of ovarian carcinoma cells [41]. The adenoviral E1A protein also lacks the binding point for the cell cycle-regulating retinoblastoma (Rb) protein. Consequently, Ad-delta24-RGD replicates selectively in cells with an inactive Rb signal transduction path and accordingly in many neoplastic cells, including ovarian carcinomas. In a phase I trial on the treatment of patients with gynaecological cancers, the intraperitoneal administration of Ad-delta24-RGD was well tolerated [42]. Replication of Ad-delta24-RGD in the patients' ascites and promising clinical activity was also demonstrated.

Challenges and Requirements of Oncolytic Therapy

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Genetic stability is important both for production technology and safety-related reasons. Ultimately, it must be possible to produce the virus easily and efficiently (i.e. with a high titre). Vaccine viruses in particular (live vaccines) satisfy these requirements. In light of the many years' experience involving enormous patient numbers, there is plenty of experience available regarding safety and side effects. Technology is available for efficient virus production with high quality requirements of the production processes, which also contribute towards a high degree of genetic stability.

One disadvantage of using vaccine viruses, however, is the high seroprevalence for the agent. With systemic application in particular, which appears to be the medium of choice for advanced cancer, oncolytic viruses are not only subjected to the innate immune response, but also to acquired defence mechanisms [43]. When treating ovarian cancer, the frequent loco-regional disease spread lends itself to intraperitoneal application. Although anti-viral antibodies may be present in malignant ascites, a phase I study shows that the intraperitoneal use of measles vaccine viruses does not cause a rise in the antibody titre and that the tumour response does not correlate with the pre-therapeutic presence of anti-measles antibodies [24,44]. Various approaches to circumvent anti-viral immune responses have also been described. On the one hand, there are approaches which eliminate viruses by modulating the immune response, for example through the simultaneous application of immuno-suppressive substances [45,46]. Another approach is one taken naturally by many viruses: by infecting endogenous, circulating cells, they mask themselves from the immune system. In an analogy to this, oncolytic viruses can be administered in carrier cells and delivered to the primary tumour concealed ("Trojan Horses") [47]. This will ensure that the agent is no longer recognised by the immune system. Viral replication can also take place within the "Trojan", and the carrier cells can contribute towards the tumour selectivity by selecting cells with inherent tumour tropism [48].

The consequences of the immune response, however, do not all have a negative effect on the effectiveness of virotherapy. The interaction of the immune system with virus-infected cells appears to contribute to the oncolytic activity in vivo and in particular induce positive long-term effects by stimulating the anti-tumour immune defence. These effects can be amplified by cloning transgenic immuno-modulators into the viral genome. The problem when investigating interactions of oncolytic viruses with the immune system, however, is that immune-compromised Xenograft mice are frequently used as the tumour model. Extensive translational research in the context of clinical trials to characterize immuno-virotherapeutic effects is therefore essential and is one main interest of the German Consortium for Translational Cancer Research (DKTK), which is currently being set up. In an innovative clinical approach led by A. Hemminki (Advanced Therapy

Access Program), patients with advanced, solid tumours that are refractive to treatment (including patients with ovarian cancer) are treated with adenoviruses that express GMCSF (Granulate Macrophage Colony Stimulating Factor) [49, 50]. GMCSF stimulates the anti-tumour immune response by activating $CD8^+$ T lymphocytes and natural killer cells. The treatment is tolerated well and has positive effects in the majority of the patients treated. There is also an anti-tumour as well as an anti-viral immune response. This in particular indicates that the immunological tolerance to tumour tissue can be broken through by oncolytic viruses.

Summary and Outlook

Virotherapy is a highly promising approach to treat ovarian cancer. Several clinical trials have demonstrated the therapy's clinical effectiveness. Unlike intraperitoneally administered chemotherapy, intraperitoneal virus administration is tolerated very well [51]. The wholly different method of action compared to that of classic cytostatics means on the one hand that tumours resistant to chemotherapy could be sensitive to oncolytic viruses [52, 53]. On the other hand, the occurrence of negative side effects is not anticipated when combined treatment involving oncolytic viruses and classical forms of treatment is given. Oncolytic viruses are also of interest as a vehicle for therapeutic transgenes in relation to a whole variety of genetic therapy constructs. As well as generating oncolytic viruses that are optimised for the treatment of ovarian cancer, future studies should also analyse the ideal form of virus administration, the identification of potential therapeutic combination partners and the interaction of virotherapy with the immune system of affected patients.

Conflict of Interest

None.

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